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The Effect of Rate Control on Quality of Life in Patients With Permanent Atrial Fibrillation

Data From the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) Study

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Objectives The aim of this study was to investigate the influence of rate control on quality of life (QOL).

Background The RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) trial showed that lenient rate control is not inferior to strict rate control in terms of cardiovascular morbidity and mortality. The influence of stringency of rate control on QOL is unknown.

Methods In RACE II, a total of 614 patients with permanent atrial fibrillation (AF) were randomized to lenient (resting heart rate [HR] <110 beats/min) or strict (resting HR <80 beats/min, HR during moderate exercise <110 beats/min) rate control. QOL was assessed in 437 patients using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) questionnaire, AF severity scale, and Multidimensional Fatigue Inventory-20 (MFI-20) at baseline, 1 year, and end of study. QOL changes were related to patient characteristics.

Results Median follow-up was 3 years. Mean age was 68 ± 8 years, and 66% were males. At the end of follow-up, all SF-36 subscales were comparable between both groups. The AF severity scale was similar at baseline and end of study. At baseline and at end of study there were no differences in the MFI-20 subscales between the 2 groups. Symptoms at baseline, younger age, and less severe underlying disease, rather than assigned therapy or heart rate, were associated with QOL improvements. Female sex and cardiovascular endpoints during the study were associated with worsening of QOL.

Conclusions Stringency of heart rate control does not influence QOL. Instead, symptoms, sex, age, and severity of the underlying disease influence QOL. (Rate Control Efficacy in Permanent Atrial Fibrillation; NCT00392613) (J Am Coll Cardiol 2011;58:1795–803) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) causes symptoms such as palpitations, dyspnea, and fatigue (1,2). Quality of life (QOL) is reduced in patients with AF compared with healthy subjects (3,4). Restoration and maintenance of sinus rhythm improve QOL (4–7), but sinus rhythm can be maintained in a minority of patients (8–10). The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation) trials showed no improvement in cardiovascular morbidity and mortality and QOL during a rhythm control strategy (8,9). Therefore, rate

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Abbreviations and Acronyms

AF = atrial fibrillation
IQR = interquartile range
MFI-20 = Multidimensional Fatigue Inventory-20
QOL = quality of life
SF-36 = 36-item Short-Form Health Survey

control has become first-choice therapy in elderly patients without severe symptoms. The optimal level of heart rate control, however, was unknown. Recently, the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient and Strict Rate Control II) trial revealed that lenient rate control is as effective as strict rate control with respect to morbidity and mortality (11,12). Strict rate control may improve QOL due to a reduction of the heart rate. However, more negative dromotropic drugs and higher doses may reduce this positive effect on QOL.

We hypothesized that QOL is comparable between lenient and strict rate control. The aim of this predefined substudy of the RACE II trial was to assess the effect of stringency of heart rate control on QOL measured with general health, AF-specific, and fatigue questionnaires (13). In addition, we investigated patient characteristics associated with a low QOL at baseline and changes in QOL during follow-up.

Methods

Patient population. This study was performed in patients with permanent AF included in the RACE II study (11,13). The institutional review board of each participating hospital approved the study, and all patients provided written informed consent. We included 614 patients who were randomized to lenient rate control (resting heart rate <110 beats/min) or strict rate control (resting heart rate <80 beats/min and heart rate <110 beats/min during moderate exercise). Rate control was instituted with beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin, alone or in combination and at various doses, until the target heart rate was achieved (13). Drug use at the end of the dose-adjustment phase was used as baseline medication in the present analysis. The primary outcome in the main study was a composite of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation. The arrhythmic events were analyzed for the purpose of the present substudy as the occurrence of any composite arrhythmic endpoint. Both strategies were associated with a comparable rate of cardiovascular adverse events. Patients were excluded from the present analyses when they did not complete one of the QOL questionnaires during follow-up (64 patients in the lenient control group and 78 patients in the strict control arm). Patients who died during the study were also not included in the analysis (17 patients in the lenient control group and 18 in the strict control group). Minimum follow-up was 2 years, and maximal follow-up was 3 years. Median follow-up was 3 years (interquartile range [IQR]: 2.2 to 3.1 years). Results of the questionnaires at baseline, 12 months, and end of study are presented. Importantly, the 12 months of follow-up were the first measurement of QOL after the dose-adjustment phase.

Baseline characteristics were comparable between the excluded patients and included patients. Baseline characteristics of the included patients are shown in Table 1. With the exception of a higher prevalence of coronary artery disease and use of statins in the lenient control group, baseline characteristics were comparable between groups. After the dose-adjustment phase, 98% of the patients in the lenient control group met the heart rate target versus 76% in the strict control group. Patients randomized to strict rate control used more and higher dosages of negative dromotropic drugs compared with the rate in the lenient control group (Table 1). During the total follow-up, heart rate was significantly higher in the lenient control group compared with the strict control group (after dose adjustment 93 ± 8 beats/min vs. 76 ± 11 beats/min; at 1 year 84 ± 13 beats/min vs. 74 ± 12 beats/min; at end of study 84 ± 14 beats/min vs. 75 ± 14 beats/min [all $p < 0.05$]).

QOL questionnaires. General health–related QOL was measured by using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).

The SF-36 is a standardized, validated, general health survey that has been used frequently in arrhythmia studies (14). The SF-36 has been translated and validated in the Netherlands (15). It contains items to assess physical health (general health perception, physical functioning, and role limitations due to physical problems and bodily pain) and mental health (social functioning, role limitations due to emotional problems, mental health, and vitality). The items for general health perception and vitality assess both physical and mental health. Each scale is composed of a number of multiple choice questions. For each of the 8 subscales, scores are transformed to a scale ranging from 0 to 100, with lower scores representing lower QOL.

Severity of AF-related symptoms was assessed using the University of Toronto AF Severity Scale (AF severity scale) (3,16,17), a disease-specific instrument intended to measure the patient's perception of severity of arrhythmia-related symptoms. This 7-item questionnaire includes common AF symptoms (e.g., palpitations, dyspnea). Items are rated on a 6-point scale. Scores range from 0 to 35, with higher scores indicating greater AF symptom severity.

Severity of fatigue was measured using the Multidimensional Fatigue Inventory-20 (MFI-20) (18,19). The MFI-20 is a self-report instrument containing 20 statements covering different aspects of fatigue. The 20 items are organized in 5 scales: general, physical and mental fatigue, and reduced activity and motivation. Scores range from 4 to 20, with the scales balanced to reduce influence of response tendencies.

Table 1 Baseline Characteristics

Characteristic	Lenient Rate Control (n = 230)	Strict Rate Control (n = 207)	Total Population (N = 437)
Age (yrs)	69 ± 7	68 ± 8	68 ± 8
Male	157 (68.3)	133 (64.3)	290 (66.4)
Total atrial fibrillation duration (months)	17 (6–54)	19 (6–58)	18 (6–58)
Duration permanent atrial fibrillation (months)	3 (1–6)	3 (1–5)	3 (1–6)
Heart rate in rest (beats/min)	95 ± 14	95 ± 11	95 ± 12
Hypertension	144 (62.6)	120 (58.0)	264 (60.4)
Coronary artery disease	53 (23.0)	30 (14.5)*	83 (19.0)
Valvular heart disease	44 (19.1)	45 (21.7)	89 (20.4)
Chronic obstructive pulmonary disease	25 (11.6)	26 (14.2)	51 (12.9)
Diabetes mellitus	21 (9.1)	19 (9.2)	40 (9.2)
Lone atrial fibrillation†	5 (2.2)	6 (2.9)	11 (2.5)
Previous heart failure hospitalization	19 (8.3)	18 (8.7)	37 (8.5)
$CHADS_2$ score‡	1.3 ± 1.0	1.3 ± 1.1	1.3 ± 1.0
0 or 1	143 (62.2)	139 (67.2)	282 (64.5)
2	64 (27.8)	43 (20.8)	107 (24.5)
3–6	23 (10.0)	25 (12.1)	48 (11.0)
Symptoms	127 (61.4)	127 (55.2)	254 (58.1)
Palpitations	47 (20.4)	59 (28.5)*	106 (24.3)
Dyspnea	77 (33.5)	84 (40.6)	161 (36.8)
Fatigue	65 (28.3)	69 (33.3)	134 (30.7)
New York Heart Association functional class			
I	153 (66.5)	124 (64.0)	277 (65.1)
II	64 (27.8)	75 (36.32)	139 (31.8)
III	13 (5.7)	8 (3.9)	21 (4.8)
Echocardiographic parameters (mm)			
Left atrial size, long-axis	46 ± 7	46 ± 7	46 ± 7
Left ventricular end-diastolic diameter	51 ± 7	51 ± 7	51 ± 7
Left ventricular end-systolic diameter	36 ± 8	36 ± 9	36 ± 8
Left ventricular ejection fraction	52 ± 11	53 ± 12	53 ± 11
≤40%	28 (12.2)	32 (15.5)	60 (13.7)
Heart rate distribution at the end of the dose adjustment phase (beats/min)			
<70	1 (0.4)	45 (21.7)	46 (22.2)
70–80	4 (1.8)	119 (57.5)	123 (59.2)
81–90	81 (35.2)	24 (11.6)	105 (46.8)
91–100	93 (40.4)	11 (5.3)	104 (45.7)
>100	51 (22.2)	8 (3.9)	59 (26.0)
Rate control medications used at the end of the dose-adjustment phase			
No rate control drugs	24 (10.4)	2 (1.0)	26 (6.0)
Beta-blocker alone	99 (43.0)	46 (22.2)	145 (33.2)
Verapamil/diltiazem alone or digoxin	13 (5.7)/18 (7.8)	11 (5.3)/1 (0.5)	24 (5.5)/19 (4.4)
Beta-blocker + verapamil/diltiazem or digoxin	7 (3.0)/45 (19.6)	25 (12.1)/79 (38.2)	32 (7.3)/124 (28.4)
Verapamil/diltiazem + digoxin	13 (5.7)	24 (11.6)	37 (8.5)
Beta-blocker + verapamil/diltiazem + digoxin	1 (0.4)	14 (6.8)	15 (3.4)
Sotalol or amiodarone	10 (4.4)	5 (2.4)	15 (3.4)
Dose (mg) (no. of patients)			
Beta-blocker (normalized to metoprolol-equivalent doses)	119 ± 81 (153)	169 ± 87 (166)	145 ± 88 (319)
Verapamil	183 ± 56 (30)	221 ± 102 (69)	209 ± 92 (99)
Diltiazem	230 ± 87 (4)	233 ± 52 (6)	232 ± 63 (10)
Digoxin	0.19 ± 0.8 (82)	0.21 ± 0.9 (120)	197 ± 83 (202)
Other medications in use at the end of the dose-adjustment phase			
ARB or ACE inhibitor	122 (53.0)	100 (48.3)	222 (50.8)
Diuretic	98 (42.6)	81 (39.1)	179 (41.0)
Statin§	82 (35.7)	51 (24.6)*	133 (30.4)
Vitamin K antagonist	228 (99.1)	203 (98.1)	431 (98.6)
Aspirin	2 (0.9)	4 (1.9)	6 (1.4)

Values are expressed as mean ± SD or n (%). *$p < 0.05$ compared with lenient rate control. †Defined as atrial fibrillation in the absence of cardiovascular disease and extracardiac precipitating causes of atrial fibrillation. ‡A measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6, with higher scores indicating a greater risk. Congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all points for a given patient. §Statins were defined as 3-hydroxy-3-methylglutaryl-coenzym A reductase inhibitors.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Statistical analysis. To analyze patient characteristics associated with low QOL at baseline, patients with low scores (scores lower than the mean value −1 SD) were identified. To assess relevant changes over time in SF-36 subscales, the changes over time were divided into relevant and irrelevant. A relevant change was pre-defined for each SF-36 subscale. The relevant change was based on the number of steps the patient improved or worsened on the stepwise multiple choice questions that comprised each SF-36 subscale between baseline and end of study (4). The following changes in individual patients were regarded as relevant: 1 step for role limitation due to physical problems and role limitations due to emotional problems, 2 steps for social functioning and bodily pain, and 3 steps for general health perception, physical functioning, mental health, and vitality. Based on the aforementioned definition of relevant changes in the SF-36 subscales, the relevant effect size of each SF-36 subscale was defined as 0.58 SD or higher from baseline (20). Also, for the AF severity scale and the MFI-20, a relevant change was defined as an effect size of >0.58 SD in these questionnaires. This is in accordance with the literature, which defines an effect size between 0.50 and 0.80 SD as a moderate change (20).

Clinical correlates of change in QOL, including clinical baseline and follow-up characteristics, were determined. The use of beta-blockers was included in this analysis because these agents effectively reduce heart rate but may reduce exercise capacity and induce fatigue (21). Use of other negative dromotropic drugs or a combination of negative dromotropic drugs and dosages were not included in this analysis because randomization strategy was our variable of interest, not different types or combinations of negative dromotropic drugs. Furthermore, because of the high number of possible combinations of negative dromotropic drugs and dosages, this would inappropriately complicate the analysis.

To examine changes over time for each QOL questionnaire and subsequent subscale, the method of repeated measures was performed. For comparison of scores between groups, a general linear model and the Student *t* test for independent variables was used. Variables with a non-normal distribution were tested with the Mann-Whitney and the Wilcoxon tests. Correlation between heart rate and QOL was assessed using the Pearson correlation. The univariate chi-square test and Student *t* test for independent variables, followed by multivariate stepwise logistic regression analyses, were performed to determine predictors of relevant QOL change over follow-up. Baseline characteristics, high baseline heart rate (>100 beats/min) in combination with a relevant (>20% heart rate reduction), occurrence of a primary endpoint, and symptoms during the study were univariately tested in a logistic regression model. All univariate predictors with $p < 0.1$ were tested in a multivariate logistic regression model using a stepwise approach. In the multivariate model, a variable was excluded when $p \geq 0.05$. In all analyses, a value of $p < 0.05$ was considered statistically significant. All analyses were performed on an intention-to-treat basis.

Results

Symptoms of AF during the study. At baseline, 58% of patients experienced symptoms of AF, predominantly dyspnea, fatigue, and palpitations (Table 1). At end of study, 48% of patients experienced symptoms of AF (dyspnea in 139 [32%], fatigue in 110 [25%], and palpitations in 49 [11%] patients). There were no differences in symptoms of AF at either baseline or at end of study between the lenient and strict control groups (Fig. 1).

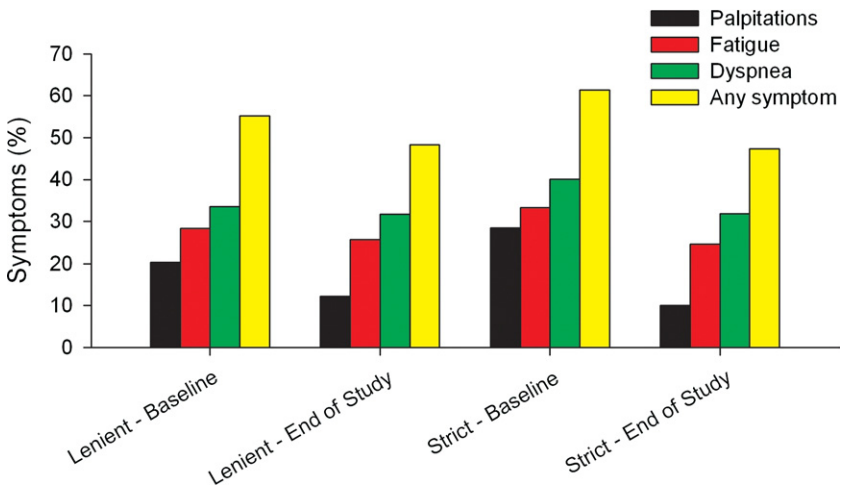

Figure 1 Percentage of Patients With Any Symptom

Symptoms of atrial fibrillation during the study, displayed by randomization strategy at baseline and end of study.

Table 2 SF-36 Score

SF-36 Subscale	Strategy	Baseline	12 Months	End of Study	Relevant Improvement From Baseline to End of Study (%)	Relevant Worsening From Baseline to End of Study (%)
General health	Lenient	59 (17)	58 (18)	59 (19)	19	16
	Strict	58 (18)	59 (18)	58 (19)	16	23
Physical functioning	Lenient	70 (22)	69 (23)	65 (25)*	13	24
	Strict	64 (25)	68 (24)*	62 (27)*	17	26
Physical role limitation	Lenient	64 (42)	62 (42)	69 (41)	24	24
	Strict	58 (42)	68 (40)*	60 (44)	28	24
Bodily pain	Lenient	84 (20)	84 (22)	81 (22)*	14	21
	Strict	81 (22)	83 (21)	80 (23)	16	17
Mental health	Lenient	79 (17)	79 (16)	79 (18)	22	18
	Strict	81 (15)	81 (14)	81 (14)	18	24
Social functioning	Lenient	84 (20)	85 (18)	84 (21)	15	13
	Strict	82 (21)	84 (21)	81 (22)	17	15
Emotional role limitation	Lenient	78 (36)	79 (36)	82 (33)	21	17
	Strict	78 (36)	81 (14)	81 (34)	22	13
Vitality	Lenient	66 (20)	65 (18)	64 (21)	17	23
	Strict	64 (19)	64 (19)	63 (20)	16	19

*$p < 0.05$ compared with baseline score.
SF-36 = Medical Outcomes Study 36-item Short-Form Health Survey.

QOL at baseline. At study entry, SF-36 scales were comparable between the lenient and strict control groups (Table 2). Low SF-36 subscales scores (scores below the mean value −1 SD) at baseline were associated with the presence of symptoms (all SF-36 subscales), diabetes mellitus (subscale general health), and female sex (subscales physical functioning, physical role limitation, bodily pain, social functioning, and vitality). At baseline, no significant differences between the lenient (6 [IQR: 3 to 11]) and strict (7 [IQR: 3 to 12]) control groups existed in AF severity scale. High AF severity scale scores (indicating more symptoms of AF) at baseline (scores above the mean value +1 SD) were associated with symptoms of AF and female sex.

All subscales of the MFI-20 were comparable between both groups at baseline (Table 3). High scores (scores above the mean value +1 SD) on the MFI-20 subscales, indicating more symptoms of fatigue, were associated with symptoms of AF at baseline (general fatigue, physical fatigue, reduced activity, and reduced motivation), and female sex (physical fatigue and reduced activity). There was also no difference in QOL, in any of the questionnaires used, between patients with a high baseline heart rate (>100 beats/min) versus those with a normal baseline heart rate (data not shown).

Changes in QOL from baseline to end of study. In the lenient control group, no significant differences were found between baseline and 12 months' follow-up in the SF-36. However, at study end, the subscales physical functioning and bodily pain significantly worsened compared with baseline (Table 2). In the strict control group, at 12 months of follow-up, physical functioning and role limitations due to physical problems improved (Table 2). At 12 months of follow-up and at the end of study, no differences were present between the lenient and strict control groups in any of the SF-36 subscales (Table 2). There were also no significant correlations between heart rate at baseline, at the end of the dose-adjustment phase nor end of study, and the SF-36 subscales scores of baseline and study end, respec-

Table 3 MFI-20 Scores

Factor	Strategy	Baseline	12 Months	End of Study	Relevant Improvement From Baseline to End of Study (%)	Relevant Worsening From Baseline to End of Study (%)
General fatigue	Lenient	11 ± 5	11 ± 5	12 ± 5	21	24
	Strict	11 ± 5	11 ± 5	12 ± 5	19	22
Physical fatigue	Lenient	11 ± 5	11 ± 5	11 ± 5	17	27
	Strict	11 ± 5	11 ± 5	12 ± 5	21	25
Reduced activity	Lenient	11 ± 5	10 ± 4	11 ± 4	22	24
	Strict	11 ± 5	11 ± 4	11 ± 5	20	26
Reduced motivation	Lenient	10 ± 4	9 ± 4	10 ± 4	20	24
	Strict	10 ± 4	9 ± 4	10 ± 4	17	30
Mental fatigue	Lenient	8 ± 4	8 ± 4	9 ± 4	16	26
	Strict	7 ± 4	8 ± 4	8 ± 4	15	25

Values are expressed as mean ± SD or %.
MFI-20 = Multidimensional Fatigue Inventory–20.

tively. There was also no relation with heart rate and changes in QOL. Comparable percentages of patients showed a relevant improvement or worsening from baseline to end of study in the different subscales. All effect sizes were <0.25, indicating small changes from baseline to end of study.

There were no significant differences in AF severity scale in either the lenient (6 [IQR: 3 to 11]) or the strict (6 [IQR: 3 to 11]) control group between baseline and end of study. At the end of follow-up, the AF severity scale was comparable between groups. At baseline and at end of study, no correlation was found between heart rate and the AF severity scale. The relevant changes in the AF severity scale were comparable in the lenient (improvement 22%; worsening 26%) and strict (improvement 26%; worsening 21%) control groups. All effect sizes (i.e., measurement of the magnitude of change over time) were 0, indicating no changes from baseline to end of study.

From baseline to 12 months of follow-up and until study end, there were no significant differences in either rate control strategy in any of the MFI-20 subscales. There were also no differences between the lenient and strict control groups during total follow-up (Table 3). The MFI-20 subscales at baseline and end of study were not correlated with heart rate at baseline, at the end of the dose-adjustment phase, or at end of study. All effect sizes were ≤0.25, indicating small changes from baseline to end of study.

Determinants of changes in QOL. We investigated whether rate control strategy, baseline characteristics, and follow-up parameters were associated with relevant changes in QOL in each questionnaire and their subscales. The parameters considered in this analysis were underlying disease, echocardiographic parameters at baseline, change in left ventricular ejection fraction from baseline to end of study, symptoms, heart rate at the end of the dose-adjustment phase, relevant heart rate reduction of a high baseline heart rate (>100

Table 4 Patient Characteristics Associated With a Relevant Improvement or Worsening in SF-36 Scores from Baseline to End of Study

Factor	Subscale	Determinants of Change in Quality of Life	OR (95% CI)	p Value
Improvement in SF-36	General health	No symptom at end of study	1.7 (1.0–3.0)	0.049
	Physical functioning	—	—	—
	Physical role limitation	Any symptom at baseline	2.0 (1.2–3.4)	0.013
		LVEF per 10%	1.3 (1.0–1.7)	0.021
		Septum per mm	0.9 (0.8–1.0)	0.043
	Bodily pain	Any symptom at baseline	2.2 (1.2–3.9)	0.010
		LVEF per 10%	1.3 (1.0–1.8)	0.032
	Mental health	—	—	—
	Social functioning	Any symptom at baseline	2.2 (1.2–4.0)	0.007
		Age per 10 yrs	0.6 (0.4–0.9)	0.007
	Emotional role limitation	Any symptom at baseline	2.7 (1.5–4.6)	<0.001
	Vitality	—	—	—
Worsening in SF-36	General health	Any symptom at end of study	2.5 (1.4–4.3)	0.002
		Diabetes mellitus	2.4 (1.0–5.0)	0.041
		Septum per mm	1.1 (1.0–1.3)	0.034
	Physical functioning	Any symptom at end of study	2.0 (1.2–3.2)	0.007
		Age per 10 yrs	1.7 (1.2–2.5)	0.003
	Physical role limitation	Any symptom at end of study	1.9 (1.1–3.1)	0.017
		Age per 10 yrs	1.6 (1.1–2.3)	0.016
	Bodily pain	Any symptom at end of study	2.0 (1.2–3.3)	0.007
	Mental health	Any symptom at end of study	2.1 (1.2–3.6)	0.011
		Female	2.3 (1.3–4.2)	0.004
		LVEF per 10%	0.7 (0.5–0.9)	0.004
		Major bleeding during study	5.0 (1.7–23.7)	0.041
	Social functioning	Any symptom at end of study	2.0 (1.1–3.5)	0.023
		Previous hospitalization for HF	2.7 (1.1–6.2)	0.025
		Arrhythmic event during study*	4.4 (1.2–15.8)	0.024
		Beta-blocker use	2.6 (1.4–4.6)	0.002
	Emotional role limitation	Any symptom at end of study	1.9 (1.1–3.3)	0.027
		Previous hospitalization for HF	2.6 (1.1–5.9)	0.024
	Vitality	Any symptom at end of study	2.0 (1.2–3.2)	0.008

*Defined as syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation.

CI = confidence interval; HF = heart failure; LVEF = left ventricular ejection fraction; OR = odds ratio; SF-36 = Medical Outcomes Study 36-item Short-Form Health Survey.

beats/min in combination with ≥20% reduction from baseline to the end of the dose-adjustment phase), and occurrence of a primary endpoint and one of the composites of the primary endpoint (hospitalization for heart failure, stroke, major bleeding, and arrhythmic events).

Symptoms at baseline, absence of symptoms at end of study, higher left ventricular ejection fraction, lower age, and a thinner septum were determinants of improvement of the SF-36 (Table 4). Worsening of the subscales of the SF-36 were associated with the presence of symptoms at end of study, higher age, diabetes mellitus, thicker septum, female sex, lower left ventricular ejection fraction, beta-blocker use, hospitalization for heart failure, major bleeding, and an arrhythmic event during the study (Table 4). Improvements in the AF severity scale were associated with symptoms at baseline (odds ratio [OR]: 4.1 [95% confidence interval (CI): 2.2 to 7.4], $p < 0.001$) and lower age (per 10-year OR: 0.7 [95% CI: 0.5 to 0.9], $p = 0.019$). Worsening in the AF severity scale were associated with symptoms at end of study (OR: 3.1 [95% CI: 1.8 to 5.3], $p < 0.001$). Worsening of the subscales of the MFI-20 were associated with the presence of symptoms at end of study, higher age, diabetes mellitus, thicker septum, female sex, and lower left ventricular ejection fraction (Table 5). Improvements and worsening were not associated with heart rate at the end of the dose-adjustment phase or randomization strategy in any of the questionnaires used. In addition, a relevant heart rate reduction was not associated with improvements or worsening of QOL in any of the study questionnaires.

Discussion

The present analysis of the RACE II study suggests that stringency of rate control does not affect QOL during treatment of patients with permanent AF. Of note, heart rate was not related to formal QOL measures, both at inclusion and follow-up. In contrast, straightforward clinical AF symptoms was related to formal QOL measures, both at inclusion as well as during follow-up. However, symptoms were not affected by stringency of rate control, and therefore the type of rate control did not affect QOL. During follow-up, minor changes in QOL occurred, but stringency of rate control again was not influential. Instead, changes in QOL were related to age, symptoms at baseline and at end of study, severity of underlying disease, and female sex.

QOL in permanent AF. Compared with healthy subjects, QOL is reduced in patients with AF (3,4). Previous studies in patients with AF have shown that QOL is comparable between rhythm and rate control strategies (4,5), although sinus rhythm is associated with an improvement in QOL (4,6,7). There are, however, no prospective studies on the effect of stringency of rate control on QOL. In a post-hoc analysis of AFFIRM, no significant relation between heart rate and QOL was found (22). A comparable subanalysis in the rate control arm of the first RACE study also showed no relation between achieved heart rate and QOL (23). We also did not observe, in any of the questionnaires used in the present analysis, a relation between heart rate and QOL, or rate control strategy and QOL, at baseline or at study end. In contrast, QOL was influenced by age, symptoms at baseline and at end of study, severity of underlying disease, and female sex.

Why do heart rate and stringency of heart rate control not affect QOL in AF? One explanation from our data is that patients with permanent AF may lack typical AF symptoms (24). In our study cohort, almost half of the patients did not have AF-related symptoms, and overall patients were not highly symptomatic (see following details). The lack of

Table 5 Patient Characteristics Associated With a Relevant Improvement or Worsening in MFI-20 From Baseline to End of Study

Factor	Subscale	Determinants of Change in Quality of Life	OR (95% CI)	p Value
Improvement in MFI-20	General fatigue	—	—	—
		—	—	—
	Physical fatigue	—	—	—
	Reduced activity	—	—	—
	Reduced motivation	—	—	—
	Mental fatigue	LVEF per 10%	0.8 (0.6–1.0)	0.033
Worsening in MFI-20	General fatigue	Any symptom at end of study	2.5 (1.5–4.2)	<0.001
		Age per 10 yrs	1.4 (1.0–2.0)	0.045
	Physical fatigue	Any symptom at end of study	2.2 (1.4–3.7)	0.002
		No symptoms at baseline	1.7 (1.0–2.8)	0.036
		Age per 10 yrs	1.6 (1.1–2.3)	0.008
		No CAD	3.1 (1.6–6.3)	0.001
	Reduced activity	Diabetes mellitus	2.9 (1.3–6.4)	0.008
		Septum per mm	1.1 (1.0–1.2)	0.036
	Reduced motivation	Age per 10 yrs	1.7 (1.2–2.4)	0.002
	Mental fatigue	Female	1.6 (1.0–2.6)	0.039

CAD = coronary artery disease; MFI-20 = Multidimensional Fatigue Inventory-20; other abbreviations as in Table 4.

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significant symptoms obviously limits the impact of rate control with respect to improving QOL, irrespective of strategy. In addition, symptoms may be driven by underlying heart disease rather than the arrhythmia itself. This finding is reflected in the fact that dyspnea and fatigue were far more frequent than typical AF-related palpitations. Finally, controlling rate does not preclude patients from being symptomatic due to ventricular irregularity and the latter may not be affected by stringency of rate control. However, our data do not rule out that strict rate control may have a beneficial effect on AF symptoms and QOL in highly symptomatic AF patients, and that, conversely, more and higher dosages of rate control drugs may have negatively affected QOL in the strict control group. This is illustrated by the association between worsening of social functioning and beta-blocker use, which may be caused by more symptoms of fatigue and a reduction in exercise capacity caused by beta-blockers (21).

Patients included in RACE II were not highly symptomatic. About 40% of the included patients did not experience any symptoms of AF. This is also reflected in the scores on the SF-36 and the MFI-20 questionnaire. However, scores of both the SF-36 and the MFI-20 were less favorable compared with the general population (15,25) but comparable to the scores found in patients with cancer (26). Patients with chronic fatigue and patients with moderate heart failure, however, had less favorable scores on the MFI-20 questionnaire compared with our patients (18,27). The relatively low symptom burden is also reflected in the scores on the AF severity scale in our study. A previous study in patients with highly symptomatic paroxysmal AF reported scores as high as 12 on the AF severity scale (19). It is well known that patients with permanent AF have symptoms less often compared with patients with paroxysmal AF (24,28). Furthermore, the type of symptoms is different between patients with paroxysmal and permanent AF. Palpitations are the main complaint in paroxysmal AF, compared with dyspnea in patients with persistent or permanent AF (28), which was also the case in our patient group. Notwithstanding these factors, presence of symptoms was related to QOL as well as changes in QOL over time, and the latter was not affected by stringency of rate control. Obviously, in highly symptomatic patients with uncontrolled heart rate well above 110 beats/min at rest, rate control would significantly affect QOL. However, our study did not focus on these highly symptomatic acute patients in whom some sort of rate control is unavoidable. Instead, we included patients with, on average, 2 to 3 months of AF with or without rate control drugs who were relatively stable. The present analysis suggests that type of rate control does not matter in terms of improvement in QOL.

Sex importantly influenced QOL. In the general population, women also showed a lower QOL (29). In addition, previous AF trials showed lower QOL in women compared with men with persistent AF (4,30,31) and with paroxysmal AF (30). In the Euro Heart Survey on Atrial Fibrillation (32) and in a Canadian cohort (33), women also had lower QOL. It is still unknown why women with AF have lower QOL. Comparable observations are known from women with a previous myocardial infarction (34). Because men are often overrepresented in clinical trials, more data on women are clearly warranted.

Study limitations. The outcome of this QOL analysis cannot be generalized to all patients with AF because all of these study patients had permanent AF and were not highly symptomatic. A trial evaluating high and low heart rates in AF would ideally bring all patients to the relevant heart rate targets. Although the differences in achieved heart rates between both groups were smaller than might have been expected, strategies to achieve the heart rate targets were completely different, which may have led to differences in QOL between groups. Although the QOL questionnaires we used are validated, it is possible that these questionnaires were not sensitive enough to detect true changes in QOL.

Conclusions

In patients with permanent AF, QOL was not affected by stringency of rate control. Instead, symptoms, female sex, age, severity of underlying disease, and occurrence of endpoints were associated with worsening of QOL.

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